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Peptoids with aliphatic sidechains as helical structures without hydrogen bonds and collagen/ inverse-collagen type structures

Fateh S. Nandel, Avneet Saini

Department of Biophysics, Panjab University, Chandigarh, India; fateh_nandel@yahoo.com

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ABSTRACT

Aliphatic homo-polypeptoids of NAla, NVal, NIle and NLeu both in the presence and absence of protecting groups adopt helical structures without hydrogen bonds with Φ, Ψ values of ~ 0, ± 90° with trans amide bonds. These structures are stabilized by carbonyl-carbonyl interactions and characterized by ~ 3.16 residues per turn with a pitch of ~ 6.13 Å. It has been shown that like polyvaline and polyleucine peptides, polypeptoids can also be exploited for the construction of potential surfactant like molecules by incorporating charged amino acid residues at the N terminal. A single-handed template with Φ, Ψ values of ~ 0, 90˚ can be attained by incorporating L-leu or L-val at the C-terminal of poly-NIle. Analysis of the simulation results in water as a function of time reveals that the opening of helical structures without hydrogen bonds takes place at sub-picosecond time scale starting from the N-terminal. This leads to the formation of collagen or *inverse*-collagen type structures (Φ, Ψ ~ -60, 145˚ and 60, -145˚ respectively) stabilized by interactions of water molecules with the backbone carbonyl groups.

Keywords: Peptoids; Conformation; Helical Structure without Hydrogen Bonds; Collagen and Inverse-Collagen Type Structures

1. INTRODUCTION

Design of polymers and oligomers that mimic complex structures and biological properties of proteins is an important endeavor with both fundamental and practical implications as polypeptides themselves are generally poor drugs, due to their *in vivo* rapid degradation by proteases and their immunogenic character [1,2]. To address multiple design criteria for applications ranging from medicinal chemistry to material science, focus is to identify non-natural chemical scaffolds that recapitulate the desirable attributes of polypeptides *i.e.* peptidomimetics. These should have good solubility in aqueous solution, access to facile sequence specific assembly of monomers containing chemically diverse side chains and capacity to form stable structures.

'Peptoids' offer attractive peptidomimetics [2] as their backbone is similar to that of peptides. Shifting of the side chain to the main chain nitrogen atom, shown in **Figure 1**, renders the alpha carbon achiral. Peptoid monomers are linked through polyimide bonds and lack the amide hydrogen; precluding the formation of hydrogen bond networks that stabilize peptide secondary structures. Their conformational behavior can be related to both proline and glycine residues. These modifications bestow protease resistance [3], while allowing suitable mimicry of the spacing between the critical chemical functionalities of bioactive peptides. Thus, it remains to be an area of active research for conformational investigations, analysis of interactions and hence, designing of molecules. In addition, the efficient sub-monomer solid phase synthesis gave a major breakthrough in peptoid research, due to the access to a large number of diverse primary amines that can be added and that too at low costs [4].

Consequently, peptoids have found application as: i)

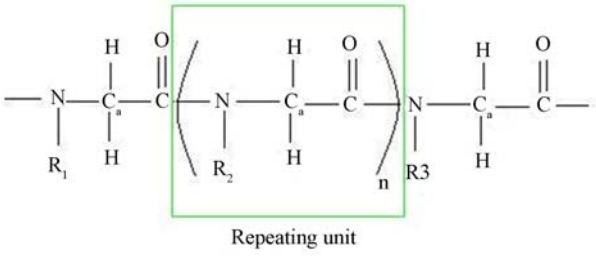


Figure 1. Primary structure of peptoid.

attractive targets for the drug discovery process [5], ii) motif for combinatorial strategies [5-10], and iii) to develop peptide mimics for biomedical applications [11-17]. They have also been exploited for their cell penetrating properties [18] and antifouling action on surfaces [19,20]. New approaches to direct the peptoid backbone towards formation of specific secondary structures such as helices (a structure in which residues rotate and rise in a repeating manner along an axis, but of what type?) are being explored for the discovery of bioactive peptoid modules [21-26].

In spite of their various applications limited systematic structural/conformational data is available on peptoids [27-29]. Peptoids comprising of 100% achiral, aromatic NPhe side chains displayed no net CD. It is not clear whether the no net CD signal is a result of degenerate conformations of opposite handedness or other structures adopted by the peptoid. It may be mentioned that even systems having no chiral centers can adopt well defined helical structures. Peptoids containing chiral aromatic side chain *i.e.* NSpe is strongly reminiscent of the alpha-helical signal on the basis of CD signatures that are almost similar to that of α-helices in peptides [30,31]. On the other hand NMR and CD studies on peptoids containing α-chiral aliphatic side chains have shown features similar to those of polyproline type helices [28]. On the basis of CD spectroscopic results it is even proposed that α-chiral aliphatic and α-chiral aromatic sidechains form helices of essentially the same type.

Thus, the conformational behavior of peptoids and the secondary structure adopted by them remains an active area of research. In this study we report the conformational preferences of both homo- and hetero-polypeptoids of the type; Ac-$(NXaa)_n$-NMe_2 of varying chain length where 'NXaa' is a peptoid residue with the amino acid side chain attached to the amide nitrogen atom by keeping the amide bond geometry both as trans or cis. The conformational results thus obtained, shall aid in the construction and design of peptoid based biomimetics.

2. METHODOLOGY

Knowledge about the global, local and low energy minima for the peptoid models Ac-NXaa-NMe_2 was obtained from the Φ, Ψ maps and χ potential energy curves that were constructed using standard bond lengths and bond angles. Input for peptoids was given in terms of internal co-ordinates *i.e.* bond lengths, torsion angles and connectivity of the atoms. Energy calculations were carried out using the semi-empirical quantum mechanical method PCILO (Pertubative Configuration Interaction using Localised molecular Orbitals) [32] and minimization was done by the variation of torsion angles. The various conformational states of all constructs were generated based on the global, local and low energy minima in the Φ, Ψ maps and χ_i, χ_j curves/maps of model peptoids and their energies computed. Minimization was further refined by varying Φ, Ψ, ω and χ values in the neighborhood of the minima in steps of 5/2 degrees. Minima obtained by PCILO calculations are also the minima at the *ab initio* level for the usual amino acids [33] and for dehydroamino acids [34-36]. In addition the PCILO results [37,38] for the peptides containing usual and unusual amino acids are in conformity with *ab initio* results [39,40] and knowledge based crystallographic data [41,42]. The charges on various atoms in different conformations of peptoid models were computed using the GRINDOL method [43].

Molecular Dynamic (MD) simulations provide great deal of information regarding the stability of peptoids in water and to the mobility of the peptoid residues. The results obtained by quantum mechanics calculations were used as the starting geometries for simulation studies using GROMACS 3.3.1 MD software package [44]. The Dundee-PRODRG2 [45] server was used to obtain the GROMACS topology and coordinate files. Interaction parameters within the design sequence were taken from GROMOS-96 force field G43a1 [46]. It is worth mentioning that the simulation results obtained by GROMOS force field are in good agreement with the experimental results [29,47 and 48]. Energy of the system was minimized by the steepest descent method, using the convergence criteria of 50 kJ mol^{-1} followed by conjugate gradient method with a force constant of 20 kJ mol^{-1}. Next, the MD run was carried out in vacuum for 20 ns, with a time step of 2 fs using the Leap Frog Algorithm. The temperature was controlled through weak coupling to a bath of constant temperature [49], using a coupling time; τ_p of 0.1ps and a reference temperature; T_0 of 300 K. LINCS algorithm [50] was used to restrict all bonds to their equilibrium lengths and the center of mass motion of the system was removed every step to maintain the effective simulation temperature at 300 K. For the evaluation of coulomb interactions and Van der Waals interaction a cut off of 0.9 and 1.0 nm respectively was applied. Long range forces were updated every 10 fs during generation of the neighbor list. The Long Range Electrostatic Interactions were calculated using a Particle Mesh Ewald Summation. Initial velocities of all atoms were taken from a Maxwellian distribution at the desired initial temperature. After the vacuum MD simulation a simple cubic periodic box was set up using the Simple Point Charge (SPC) Water Model [51]. In order to allow equilibration of solvent around the model sequence, position of all peptoid residues was restrained for 20 ps. Finally, MD simulation for 1ns at 300 K, without any restrictions was carried out. The

Table 1. Conformational results* of the various dipeptoid models.

Φ, ψ, ω χ_i, χ_j (deg)	ΔE kcal/mol	**Φ, ψ,** ω χ_i, χ_j (deg)	ΔE kcal/mol	**Φ, ψ,** ω χ_i, χ_j (deg)	ΔE kcal/mol	**Φ, ψ,** ω χ_i, χ_j (deg)	ΔE kcal/mol
Ac-NAla-NMe$_2$				Ac-NVal-NMe$_2$			
–2, 92, 180	0	**–175, 85,** 0	1.8	**0, –85,** 174 175	0	**100, 135,** –3 75	–1
–5, –80, 180	0	**180, –95,** 0	3.7	**0, 90,** 174 175	0.4	**–70, 170,** –10 120	0.7
180, –90, 180	1.8			**–95, –170,** 175 135	1.5		
180, 90, 180	1.9			**85, 175,** 170 110	2.1		
120, 180, 180	2						
–120, 180, 180	2.4						
Ac-NLeu-NMe$_2$				Ac-NIle-NMe$_2$			
15, –105, 180 130, 175	0	**–125, –170,** 0 –65, 175	3.2	**5, 85,** 180 145, 170	0	**–95, –155,** 0 155, 180	2.5
15, 70, 178 130, 175	1.5	**120, –175,** 0 65, 70	3.5	**0, –90,** 180 145, 170	0.3	**90, 180,** 0 155, 180	5.2
120, 180, 180 –110, 55	2.6	**–60, 175,** –5 115, 180	4	**–90, 180,** 180 145, 170	2.9		
–120, 180, 178 –5, –60	2.9	**55, –160,** 8 –115, 60	4.2	**90, 180,** 180 145, 170	4		

* **Φ, ψ** values are in **bold,** *ω* in *italics* and χ_i, χ_j in normal text.

pressure was controlled using weak coupling with a time constant of 0.5 ps and a reference pressure of 1 Bar.

3. RESULTS AND DISCUSSION

Conformational results in terms of Φ, Ψ, ω and χ values of the various model dipeptoids in both cis and trans amide bond geometries are summarized in **Table 1**. In general, there is not much difference in the energy of the various conformers and hence, with a change in experimental conditions different states may be populated. Results in **Table 1** also reveal that NAla can be populated in several conformations due to its simple and small side chain with no branching. Thus, incorporation of NAla in peptides may lead to disruption of helices as the energy difference between the states is small and different states may be populated depending on the environment. This observation is consistent with the experimental finding that incorporation of NAla in the otherwise helical antimicrobial peptides decreases the helical content [52].

In higher mers of all peptoid models it is apparent from the results in **Table 2** that degenerate helical structures without hydrogen bonds with Φ, Ψ values of ~ 0, + 90˚ are most stable with trans amide bond geometry. These structures characterized by n = 3.16, with a pitch of 6.13 Å have also been reported in poly-dehydro amino acids [36]. A molecular view of the models Ac-NVal$_7$-NMe$_2$ and Ac-NIle$_7$-NMe$_2$ shown in **Figure 2** with trans amide bonds for the conformational states with Φ, Ψ values ~ 0, -90˚ and 0, 90˚ respectively clearly shows pore formation with an average diameter of 4.6 Å with hydrophobic side chains protruding outwards. Such structures are maximally stable in the hydrophobic environment masking the carbonyl oxygens that point inwards towards the central cavity. Negative charge on carbonyl oxygen (~ -0.66) may provide a negative potential gradient along the pore facilitating the cation to

Table 2. Conformational results* for homo-polypeptoid models.

			Φ, ψ, ω χ_i, χ_j (deg)				ΔE kcal/mol°
1	**2**	**3**	**4**	**5**	**6**	**7**	
Ac-NAla$_6$-NMe$_2$							
–15, 105, 178	**–25, 120,** 173	**0, 90,** 172	**–25, 110,** 170	**–5, 95,** 176	**0, 95,** 170		0
-	-	-	-	-	-		
5, –95, –179	**15, –100,** –178	**10, –95,** –179	**15, –105,** 180	**5, –95,** –174	**10, –100,** –179		0.17
-	-	-	-	-	-		
Ac-NVal$_6$-NMe$_2$							
0, 90, 178	**–10, 100,** 176	**–5, 95,** 172	**–5, 95,** 174	**–5, 95,** 172	**–5, 95,** 176		0
90	95	95	90	95	90		
–5, –85, –176	**5, –95,** –172	**5, –95,** –172	**5, –95,** –172	**5, –95,** –172	**5, –95,** –176		0.66
90	145	145	150	145	150		
–90, 180, 178	**–85, 175,** 178	**–95, –175,** 178	**–65, 170,** 176	**–80, 175,** –178	**–40, 135,** 178		19.53
135	130	150	120	125	125		
90, –175, –178	**90, 175,** 180	**85, 180,** –176	**95, 170,** –176	**85, 180,** –176	**45, –145,** –178		19.55
100	100	115	100	115	120		
NVal$_6$-NH$_2$							
–, 180, 176	**0, 90,** 172	**–10, 100,** 170	**–5, 95,** 170	**–10, 100,** 172	**0, 90,** –176		0
–170	155	95	95	95	90		
–, 175, –178	**0, –90,** 180	**30, –120,** –174	**–5, –90,** –176	**30, –120,** 180	**0, –90,** 174		0.72
40	145	145	85	145	90		
Ac-NLeu$_6$-NMe$_2$							
5, 85, 176	**5, 90,** 170	**5, 90,** 168	**10, 85,** 172	**0, 90,** 176	**–5, 95,** 176		0
130, 175	120, 180	120, 175	115, 175	115, 175	115, 180		
25, –115, –177	**30, –120,** 172	**30, –120,** 177	**35, –120,** 174	**30, –120,** 170	**15, –100,** 173		3.84
130, 175	85, 75	90, 75	90, 75	90, 80	85, 85		
Ac-Nile$_7$-NMe$_2$							
5, 85, 174	**–5, 95,** 172	**–5, 95,** 172	**–5, 95,** 174	**–5, 95,** 172	**–5, 95,** 176	**0, 90,** 176	0
150, 165	95, 170	95, 175	90, 170	90, 175	90, 170	95, 170	
0, –90, –178	**5, –105,** –174	**5, –95,** –174	**10, –100,** –174	**–5, –90,** –166	**30, –120,** –174	**5, –95,** –178	0.25
110, 55	150, 170	150, 165	150, 170	145, 165	140, 170	85, 170	
Ac-NLys-NLeu$_6$-NMe$_2$							
–90, 160, 180	**5, 90,** 170	**0, 90,** 178	**10, 85,** 180	**0, 90,** 176	**–5, 95,** 176	**0, 90,** 180	0
180, 180, 160, –175	120, 180	120, 175	115, 175	115, 175	115, 180	120, 180	

* **Φ, ψ** values are given in **bold,** *ω in italics and* χ_i, χ_j in normal text.

pass through in a single file. Thus, like Gramicidin A, these peptoids may be exploited for the construction and design of channels in membranes. It is also obvious from the results in **Table 2** that presence or absence of protecting groups hardly affected the nature of the most stable conformation adopted by poly-NVal.

These helical structures without hydrogen bonds are stabilized by carbonyl-carbonyl interactions between carbonyl oxygen of i^{th} residue and carbonyl carbon of i^{th} + 1 with $d_{Oi...Ci+1}$ being 2.18 Å. A careful look at the data from penta peptoid onwards revealed that in the conformation with Φ, Ψ values of ~ 0, 90˚ all ω values lie between 168 ≤ ω ≤ 180˚ and in the conformation with Φ, Ψ values of ~ 0, - 90˚ they lie between 180 ≤ ω ≤ 194˚.The deviation in ω values resulted in stronger carbonyl interactions relative to those in complete trans amide bond geometries. In addition, C-H…O interactions between the C = O of i^{th} residue and HC_α-N of the side chain of i^{th} + 3 residue ($d_{O...H}$ and $d_{O...C}$ being ~ 2.1 and 3.0 Å) leads to the formation of an eleven membered ring (**Figure 2**). Based on a systematic study between ketonic groups in the Cambridge structure database carbonyl-carbonyl interactions [53,54] have been modeled by three main types of interaction motifs. Importance of carbonyl interactions as a stabilizing factor in α-helices, β-sheets and right-handed twist is well-documented [55,

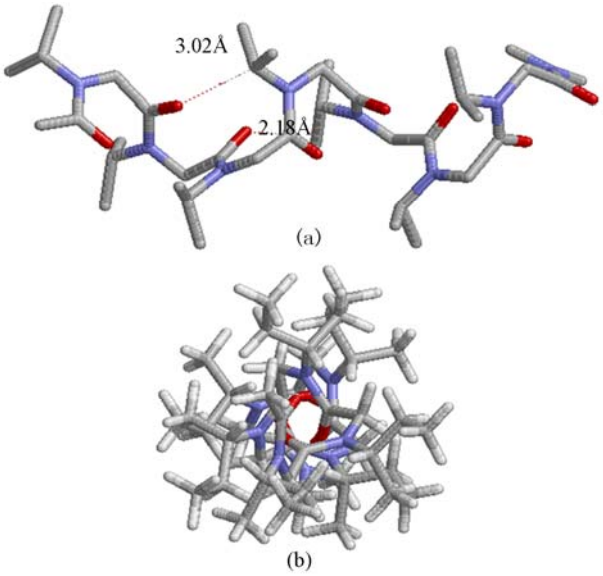


Figure 2. Molecular view of (a) Ac-$NVal_7$-NMe_2 in the conformation state with Φ, Ψ, ω values of ~ 0, -90, 180˚depicting carbonyl-carbonyl interactions and formation of an eleven member ring due to C-H…O interactions between the i^{th} and i^{th} + 3 residue; (b) Ac-$NIle_7$-NMe_2 with Φ, Ψ , ω values of ~ 0, 90, 180˚showing the formation of a hydrophilic pore with the masking of the carbonyl groups by the hydrophobic side chains.

56]. They also stabilize the partially allowed Ramachandran conformations of aspartic acid and asparagines [55] and helical structures without hydrogen bonds in peptides constructed from achiral and unusual amino acids [36,58-59].

Degenerate helical structures without hydrogen bonds with opposite handedness observed in polypeptoid models of NVal/NIle having branching at the N-C_α position implies population of both states to the same extent and hence, very well explains the very weak/no signal in CD spectroscopy for aliphatic peptoids [28]. Interestingly, for poly-NLeu only one state with Φ, Ψ values of ~ 0, 90 ° is predicted; possibly due to the side chain branching at the N-C_β position. Thus, the difference in the branching pattern changes the local environment and may be responsible for the difference in the conformational behavior of peptoid models.

Φ, Ψ values of 0, ± 90˚ appear to be unusual even in peptides, but this region has been predicted a minima for some amino acids [36]. Also, for the dipeptides of glycine & alanine [60] a stationary point near Φ = 0˚ , Ψ = 90˚ at the HF/3.21G and HF/6.31+G levels has been reported. Ramachandran plots based on; i) PDB- 40 dataset [61] corresponding to X-ray protein structures with the resolution of 2.5 Å or better for 470 proteins, 95778 total residues plotted, proline and glycine excluded and (ii) NMR derived structure for 113 proteins, 84719 total residues plotted, (proline and glycine excluded) show appreciable density between the left-handed helical region and the collagen-type structural region [62,63] and between the right-handed helical region and the *inverse*-collagen type structural region [60,61]. Though, the dataset for the NMR derived structures is small compared to the X-ray protein structures, yet in the mentioned regions the data point density is more for NMR derived structures *i.e.* in the solution phase. Thus, the conformational states with Φ, Ψ values of ~ 0, ± 90˚ are not an over-estimation and may be realized in solvents with low polarity.

4. CONSTRUCTION AND DESIGN OF NANO-STRUCTURES

***Single Handed Template*:** Alipihatic polypeptoids were realized in degenerate helical structures without hydrogen bonds with rise & rotation per residue of 1.94 Å and 114˚ respectively. To construct a template with a given handedness from these peptoid residues, either L/D-Leu or L/D-Val residue was incorporated either at the N-terminal or the C-terminal of the poly Nile/Nval peptoid sequences of required length. Incorporation of such chiral amino acids has been shown to control the screw sense of helical peptides constructed from achiral residues [36,58,62-63]. Therefore, these amino acids (L/D-Val or L/D-Leu having branching in the side chain) were incorporated in achiral peptoids to control the screw sense of helical structures. The conformational results thus obtained are given in **Table 3** and it is obvious that in poly-Nile peptoid models the degeneracy was lifted and only one conformation with Φ, Ψ values of ~ 0, 90˚ was realized by incorporating L-leu or L-val at the C-terminal. Incorporation of L or D-leu either at the N or C-terminal of poly-NVal sequence models did not lift the degeneracy. This may be attributed to the local environment around N-C_α, which is asymmetrical in NIle residues and symmetrical in NVal residues. Thus, NIle with its asymmetrical side chain plays a vital role in lifting the degeneracy and hence, construction of a single handed template.

Peptoids as Surfactants: The helical structures adopted by homo-polypeptoid models (NVal, NLeu, NIle) appear similar (although with different Φ, Ψ values) to the corresponding helical structures in polypeptides of leucine, valine, isoleucine and norleucine with the non-polar side chains projecting outwards forming well-defined hydrophobic structures with a hydrophilic pore. Poly-leucine, poly-valine, poly-isoleucine and poly-norleucine like peptides have shown surface activity that helped in accelerating the surface spreading at the air-water interface and thus, exhibited improved dynamic activity. Poly-leucine peptides or peptides rich in leucine have been exploited for their surfactant like properties especially in lung surfactant proteins SP-B

Table 3. Construction of a single handed template for Ac-L-leu-$(NIle)_6$-NMe_2.

			Φ, ψ, ω **χ_i, χ_j (deg)**				**ΔE kcal/mol**
1	**2**	**3**	**4**	**5**	**6**	**7**	
			Ac-L-leu-$(NIle)_6$-NMe_2				
–100, 130, –92	**10, 80,** 176	**0, 95,** 170	**–5, 95,** 172	**–5, 100,** 172	**–5, 95,** 172	**0, 90,** 174	0
–55, 170	155, 170	90, 175	95, 175	95, 175	95, 170	90, 175	
–155, 150, 90	**0, –90,** –178	**–5, –90,** –172	**5, –95,** –176	**25, –120,** –174	**0, –90,** –176	**0, –90,** –178	1.99
55, 150	150, 170	155, 160	150, 170	150, 170	90, 170	150, 170	
			Ac-$(NIle)_6$-L-leu-NMe_2				
15, 90, 90	**0, 95,** 170	**0, 95,** 170	**–15, 100,** 176	**0, 90,** 172	**15, 70,** 178	**–20, 115,** 174	0.68
140, 170	100, 170	95, 170	95, 165	90, 170	90, 175	–65, 170	
–10, –80, –86	**10, –100,** –178	**0, –95,** –170	**25, –120,** –176	**0, –90,** –176	**–5, –75,** 176	**180, 160,** –178	7.00
130, 50	145, 175	150, 165	140, 175	90, 170	155, 170	60, 140	
			Ac-$(NIle)_6$-L-val-NMe_2				
5, 85, 178	**–5, 100,** 170	**5, 90,** 166	**–15, 100,** 176	**0, 90,** 172	**5, 75,** –176	**–10, 105,** 174	0
145, 170	90, 170	100, 165	90, 160	90, 170	90, 170	180	
–5, –85, –178	**15, –105,** –176	**0, –95,** –166	**0, –95,** –170	**0, –90,** –172	**–5, –75,** 176	**–30, 115,** –170	3.56
115, 60	145, 170	150, 170	150, 160	150, 170	155, 170	50	

and SP-C [13,14]. On similar lines the corresponding peptoid mimics are constructed to design surfactant like molecules by incorporation of NLys residue at the N-terminal in poly-NLeu and the conformational results are summarized in **Table 2**. A graphical view of the peptoid in the most stable state as shown in **Figure 3** clearly depicts that NLys residue resembles the polar head group and the NLeu residues formed the hydrophobic tail like structure similar to that of lipids.

5. SIMULATION STUDIES

Simulation studies on aliphatic peptoids reveals almost

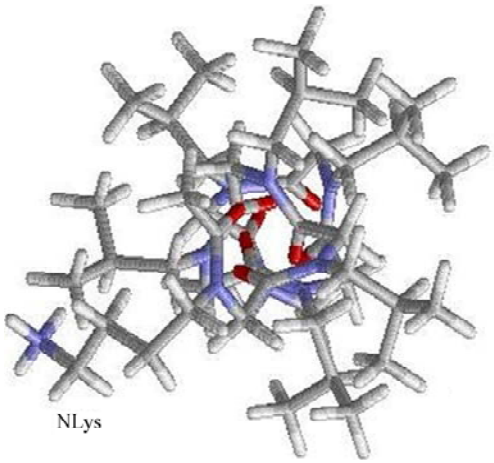


Figure 3. A graphical view of the surfactant peptoid design 'Ac-NLys-$(NLeu)_6$-NMe_2'.

similar conformational results irrespective of the initial geometry taken for simulations (*i.e.* with Φ, Ψ = 0, ± 90˚ ; ± 60, 180˚ ; or ± 120, 180˚) and the side chain. This means shifting of the side chain from the carbon alpha to the amide nitrogen makes the peptoid backbone less flexible and this observation is consistent with the experimental and computational results [29,64-65].

A molecular view of the model Ac-$NVal_7$-NMe_2 after 1ns simulation in water (with starting geometry having Φ, Ψ values of ~ 0, 90˚ and ~ 0, - 90˚) is shown in **Figure 4**. It is apparent from the results in **Table 4** and the molecular graphics shown in **Figures 4 & 5**; that the interactions of water molecules with the carbonyl oxygen of the backbone lead to the population of structures with average Φ, Ψ values around -60, 145˚ and 60, -145˚. The conformation with Φ, Ψ values of ~ -60, 145˚ is called collagen type structure [66] and the structure with inverse Φ, Ψ values of collagen type structure *i.e.* 60, -145˚ is named as *inverse*-collagen type structure. Collagen type structures are also well documented in globular proteins [67,41]. The distance between the carbonyl oxygen of the peptoid backbone and hydrogen atoms of water molecules are found to lie between 1.5 to 1.9 Å. The angle/OHO(C) are observed to lie in the range from 150 to 180˚. This observation is consistent with the experimental finding that the hydrogen bond angle in biological systems is never 180˚ but less [68]. In QM calculations both collagen and *inverse*-collagen type structures are predicted to be higher in energy (**Table 4**). Helical structures with Φ = ± 79.2˚, Ψ = ± 174.6˚ with

Table 4. Torsion angles for the peptoids in trans amide bond geometry after 1ns simulation with different starting geometries having 1) Φ, Ψ values of ~ 0°, - 90°and 2) Φ, Ψ values of ~ 0°, 90°.

	Φ	ψ	ω	χ_i, χ_j (deg)		Φ	ψ	ω	χ_i, χ_j (deg)
	Ac-NAla$_7$-NMe$_2$							Ac-NVal$_7$-NMe$_2$	
1	**72.3**	**–159.2**	178.2		**1**	**56.3**	**- 131.9**	–163.0	108.1
	107.7	**–153.3**	175.2			**61.0**	**- 143.0**	–170.8	121.6
	70.5	**–113.8**	157.7			**79.6**	**- 137.7**	158.4	138.0
	55.9	**–120.1**	175.3			**63.4**	**- 122.6**	–174.7	126.7
	57.7	**–128.4**	177.2			**64.9**	**- 125.6**	177.1	122.3
	92.4	**–137.1**	159.9			**77.5**	**- 151.2**	–175.1	122.7
	72.9	**–138.5**	179.3			**–61.4**	**99.0**	–172.5	113.3
2	**–63.8**	**148.8**	–162.6		**2**	**–49.7**	**113.9**	178.3	–104.2
	–79.4	**134.9**	–174.4			**–59.4**	**127.7**	–174.0	–118.8
	–117.7	**148.1**	–173.6			**–66.4**	**153.8**	166.6	–123.4
	–83.5	**–146.0**	163.5			**–58.5**	**128.7**	168.8	–116.0
	–90.5	**–164.7**	163.8			**–75.4**	**125.9**	–179.3	–120.9
	–104.3	**–156.7**	160.2			**–44.9**	**124.1**	–171.8	–121.4
	70.4	**–117.5**	157.2			**–76.1**	**145.4**	175.1	–104.6
	Ac-NLeu$_7$-NMe$_2$							Ac-NIle$_7$-NMe$_2$	
1	**79.8**	**166.6**	–169.6	95.5, –88.4	**1**	**65.3**	**–154.6**	–176.1	103.6, 69.4
	46.8	**–117.7**	–176.2	–90.5, 148.2		**57.8**	**–127.4**	–162.7	112.6, 71.6
	65.6	**–162.9**	–165.7	–145.6, –157.4		**78.6**	**–155.4**	–175.3	103.0, 110.6
	81.1	**–107.2**	168.0	105.1, –79.0		**64.3**	**–142.8**	–189.6	124.8, 87.6
	61.4	**–108.2**	179.6	–110.7, –162.9		**65.9**	**–135.4**	177.8	97.3, 87.4
	55.3	**–136.2**	172.4	–97.3, 78.7		**89.4**	**169.3**	–168.7	102.9, 143.5
	94.1	**–152.8**	163.2	131.6, –84.2		**66.8**	**–120.6**	–175.0	108.0, 76.5
2	**–68.2**	**133.9**	–170.5	113.5, –62.1	**2**	**–87.8**	**–169.7**	167.9	109.8, 87.9
	–67.9	**145.6**	179.5	118.1, –83.6		**–61.6**	**110.4**	177.6	131.1, 152.9
	–57.3	**123.4**	–176.0	119.7, –85.9		**–75.1**	**146.8**	–176.1	85.9, 153.6
	–72.4	**129.6**	–160.9	85.1, –117.3		**–61.8**	**152.9**	174.1	123.7, –174.6
	–64.6	**142.5**	–170.3	107.9, –70.7		**–64.5**	**145.7**	174.3	109.4, 95.6
	–76.3	**157.2**	179.4	–118.9, –98.8		**–50.8**	**135.3**	–174.1	110.6, 76.9
	–52.5	**152.8**	–174.9	115.5, –84.1		**–67.0**	**137.1**	176.5	104.9, 95.7

Table 5. Torsion angles for the model Ac-NVal$_7$-NMe$_2$ at different simulation time in water with starting conformation of Φ, Ψ, ω ~ 0°, -90°, 180°.

Time/ ps ↓	Φ, Ψ Residue number →						
	1	**2**	**3**	**4**	**5**	**6**	**7**
0.5	57.7, –149.1	68.8, –134.7	23.2, –88.7	12.8, –100.5	36.6, –112.7	17.4, –110.4	–20.9, –67.1
1.0	70.0, –152.6	62.5, –141.5	53.5, –128.9	43.2, –103.7	20.2, –96.2	68.4, –134.6	–27.7, –70.9
5.0	51.6, –137.2	70.8, 178.9	67.6, –125.4	66.5, –119.5	37.3, –100.6	62.9, –126.4	–30.2, –73.7
10.0	49.9, –123.8	73.2, 178.0	63.1, –140.2	46.8, –120.1	48.1, –133.7	67.0, –129.7	18.7, –100.6
1000.0	58.3, –131.9	61.0, –143.0	79.6, –137.7	63.4, –122.6	64.9, –125.6	77.5, –151.2	–61.4, 99.0

trans amide bond geometry for sarcosine have also been reported by *ab initio* calculations using dielectric constants to replicate an aqueous environment [69] but not in explicit solvent. Our results are also consistent with the peptoid backbone conformational landscape described by Butterfoss *et al.* using *ab initio* Gaussian03 package [29].

Opening of Helical Structure without hydrogen bonds: To gain insight into the opening of the helical structures, whether opening starts from the N or C-terminal

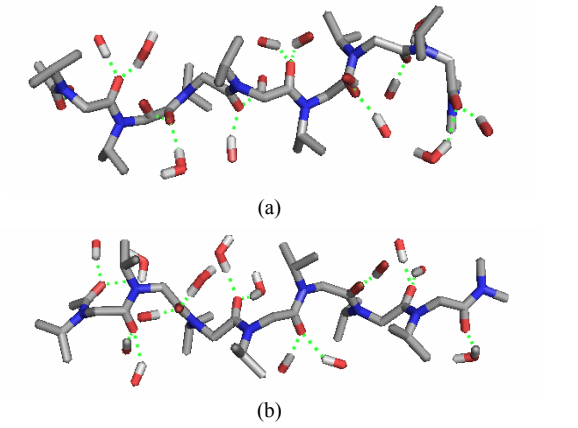


Figure 4. Molecular view of the (a) Collagen and (b) *inverse*-collagen type structures observed in the model 'Ac-NVal$_7$-NMe$_2$' after 1ns simulation in water with starting geometry having Φ, Ψ values of ~ 0, 90˚and 0, -90˚ respectively. As evident, such structures are stabilized by the interactions of water molecules with carbonyl moieties of the peptoid backbone. For clarity purposes, water molecules within 3 Å of the peptoid surface are shown.

a pictorial view of the peptoid Ac-(NVal)$_7$-NMe$_2$ at different simulation times with water molecules within 3 Å of the peptoid surface is shown in **Figure 6**. It is apparent from the graphics that the opening of the helical structure into the collagen or *inverse*-collagen type structure begins at the N-terminal due to initial interactions of water molecules with the acetyl carbonyl oxygen that lead to the change of torsion angles. Analysis of the simulation results at different time intervals given in **Table 5** reveal that opening of the helical structure without hydrogen bonds takes place at the sub picoseconds time scale. The number of hydrogen bonds formed between water molecules and the carbonyl moieties attain the maximum val ues within 10 ps and thereafter remain

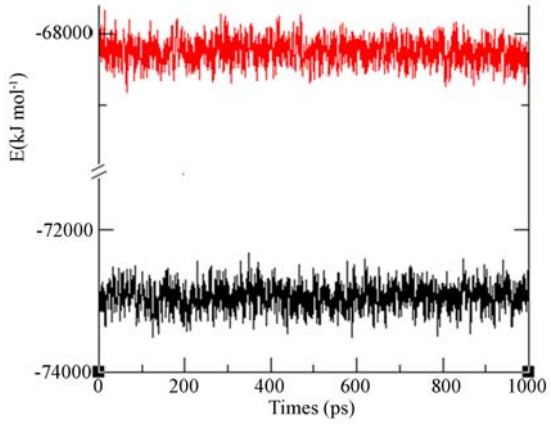


Figure 5. Plot of total energy (E) as a function of simulation time for the model Ac-(NIle)$_7$-NMe$_2$ (black) and Ac-(NLeu)$_7$-NMe$_2$ (red) for the collagen type conformations.

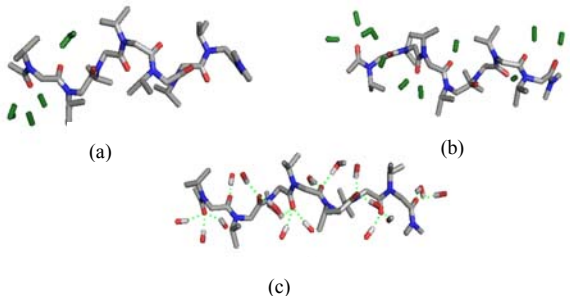
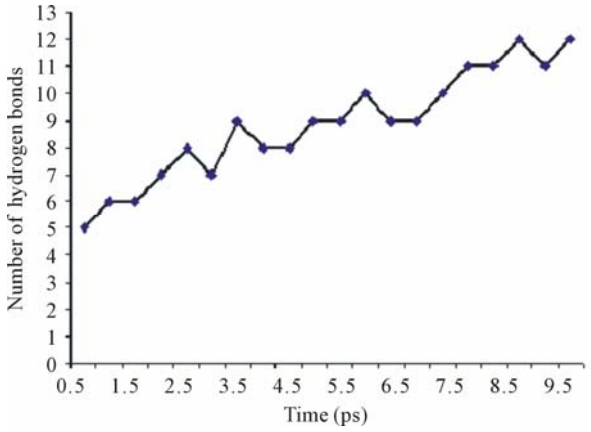


Figure 6. Snapshots of the peptoid 'Ac-(NVal)$_7$-NMe$_2$' at different simulation intervals (a) 1ps, (b) 5ps and (c) 10ps with water molecules within 3 Å of the peptoid surface indicates that the opening of the helical structure without hydrogen bonds starts at the N-terminal.

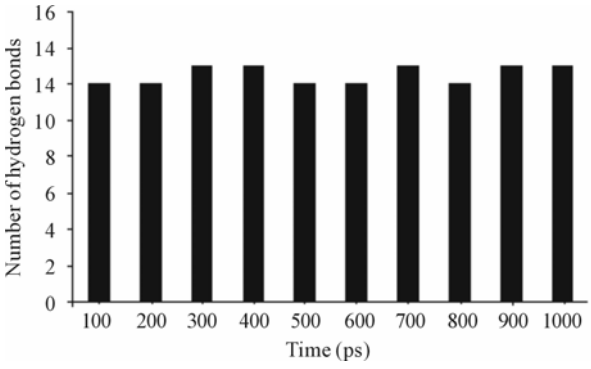
constant throughout the simulation period (**Figure 7**).

6. CONCLUSIONS

Aliphatic polypeptoid models adopt degenerate helical structures without hydrogen bonds with Φ, Ψ values of ~ 0, ± 90˚ in trans amide bond geometry that are stabilized



(a)



(b)

Figure 7. Number of hydrogen bonds formed between carbonyl groups of the backbone and water molecules for the model 'Ac-(NVal)$_7$-NMe$_2$' (a) increases within first 10 ps and thereafter, (b) remains constant on simulation in water.

by carbonyl interactions. The population of poly-NLeu in only one state with Φ, Ψ values of ~ 0, 90˚ is attributed to the difference in the side chain branching patterns of these residues. A single handed template was realized by incorporating L-leu or L-val at the C-terminal of poly-NIle sequences. Such templates provide patterns and find utility in generating a comple- mentary molecule. In peptoids, helical structures without hydrogen bonds can also be exploited for the design of surfactant molecules by incorporating charged residues at the terminal positions. Simulation studies reveal that interactions of water molecules with the carbonyl moieties of peptoid backbone act as the primary driving force behind the opening of helical structures without hydrogen bonds resulting in the population of collagen or *inverse*-collagen type structures.

7. ACKNOWLEDGMENTS

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